RESEARCH PAPER

Ammonium Chloride–Ethanol Mediated Synthesis, Characterization, and Antimicrobial Evaluation of Novel 2-substituted 5-(2-naphthyloxy)/5-Phenoxy benzimidazole Derivatives

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Abstract

An efficient and eco-friendly method was developed for the synthesis of a series of 2-substituted 5-(2-naphthyloxy)/5-Phenoxy benzimidazole derivatives using ammonium chloride (NH_4Cl) and ethanol under mild conditions. The target compounds were synthesized through the condensation of substituted o-phenylenediamine with various benzoic acids at room temperature. The reaction proceeded smoothly and was completed within 4 hours, yielding eight benzimidazole derivatives in moderate to good yields (60–80%). The use of inexpensive, readily available, and non-toxic reagents, along with simple experimental procedures, makes this method practical and sustainable. All synthesized compounds were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. The developed protocol avoids vigorous reaction conditions and costly catalysts while providing an effective route to structurally diverse benzimidazole derivatives. Owing to its simplicity, operational ease, and green nature, this methodology offers a useful approach for the synthesis of biologically relevant benzimidazole derivatives. Further synthesized compounds were tested for antibacterial and antifungal activity by tube dilution method.

Keywords: Benzimidazole, Ammonium chloride, Ethanol, Green synthesis, Room temperature, Heterocyclic compounds.

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I. Introduction

Benzimidazole is an important nitrogen-containing heterocyclic ring structure that has attracted considerable attention in medicinal and synthetic chemistry because of its wide range of biological and pharmacological activities[1]. The benzimidazole nucleus is a privileged structural motif found in numerous clinically useful drugs and bioactive molecules[2], exhibiting antibacterial, antifungal, antiviral, anticancer, anti-inflammatory, antidiabetic, and antiparasitic properties. Owing to these diverse applications, the development of efficient synthetic methodologies for benzimidazole derivatives continues to be an active area of research[3].

The biological activity of benzimidazole derivatives is strongly influenced by the nature and position of substituents attached to the benzimidazole ring system. In particular, 2-substituted benzimidazoles have demonstrated significant antimicrobial activity[4] and have emerged as promising candidates for the development of new therapeutic agents. The incorporation of phenoxy[5] and naphthyloxy[6] moieties into heterocyclic frameworks has also been reported to enhance biological activity through improved molecular interactions with biological targets.

Conventionally, benzimidazoles are synthesized through the condensation of o-phenylenediamine with carboxylic acids, aldehydes, or their derivatives in the presence of strong acids, metal catalysts, oxidizing agents, or elevated temperatures[7]. Although these methods are effective, many suffer from drawbacks such as severe reaction conditions, prolonged reaction times, toxic reagents, expensive catalysts, and generation of environmentally hazardous waste. Consequently, there is growing interest in developing greener[8] and more sustainable synthetic approaches that minimize environmental impact while maintaining synthetic efficiency[9].

Green chemistry principles emphasize the use of safer solvents, inexpensive reagents, energy-efficient processes, and eco-compatible reaction conditions[10]. Recent studies have highlighted the importance of developing catalyst systems that are economical, readily available, and less harmful to the environment[11]. Ethanol has emerged as an attractive green solvent because of its low toxicity (as per Material Safety Data Sheet), biodegradability, and renewable nature. Likewise, ammonium chloride (NH_4Cl) is inexpensive, easily available, non-toxic (as mentioned in Material Safety Data Sheet), and environmentally friendly, making it a useful additive for sustainable synthetic transformations[12].

In view of the biological significance of benzimidazole derivatives and the increasing demand for green synthetic methodologies, the present work describes the synthesis of a series of 2-substituted 5-phenoxy/naphthyloxy benzimidazole derivatives using a NH_4Cl–ethanol system under mild reaction conditions. The reactions were carried out at room temperature and successfully produced the desired products in moderate to good yields within a short reaction time. The synthesized compounds were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and mass

spectrometric methods. Furthermore, the antimicrobial potential of the synthesized derivatives was evaluated against selected bacterial and fungal strains using the tube dilution method. The developed protocol provides a simple, cost-effective, and environmentally benign approach for the preparation of structurally diverse benzimidazole derivatives with potential biological significance.

II. Materials and Methods

[A] Materials

All chemicals and solvents were of analytical grade and were used without further purification. 5-chloro-2-nitro aniline was ordered from Sigma Aldrich; substituted benzoic acids, ammonium chloride (NH_4Cl), and ethanol were obtained from Loba Chemie; & 2-Naphthol, Phenol, Potassium Carbonate, Dimethyl Formamide, Hydrazine Hydrate and Raney Nickel were procured from Spectrochem. The progress of reactions was monitored by thin-layer chromatography (TLC) on silica gel plates purchased from Merck.

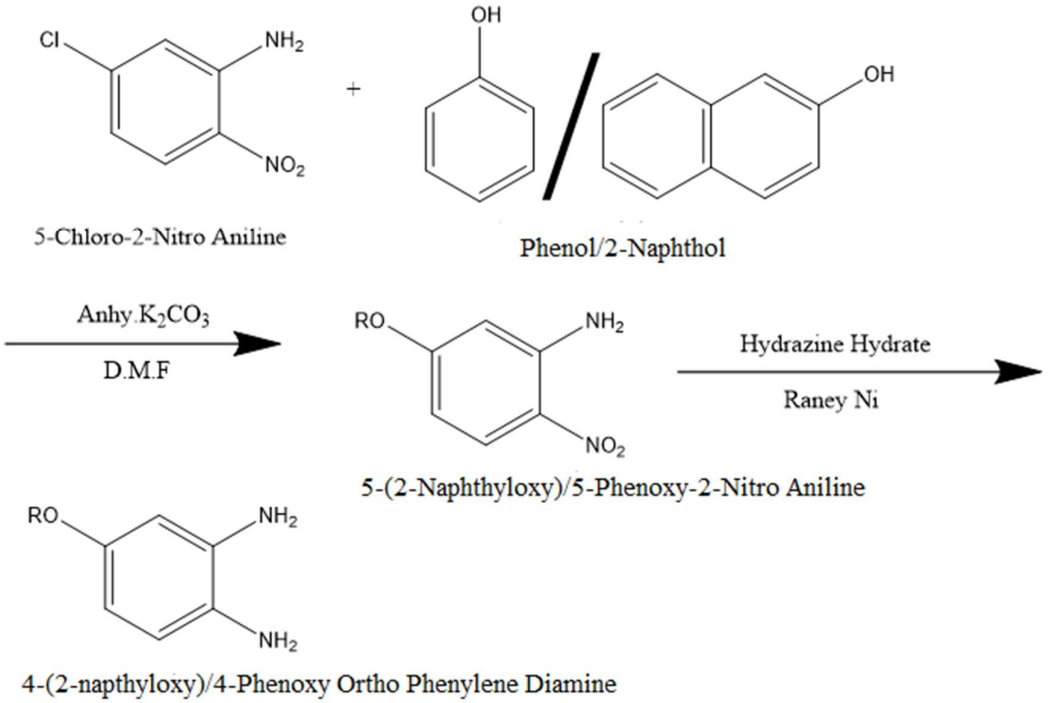
[B] Methods

Melting points were determined using an Equiptronics EQ-730 instrument and are uncorrected. Thin-layer chromatography (TLC) was carried out on silica gel plates, and the spots were visualized under UV light at 254 nm. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer using DMSO-d_6 as the solvent and tetramethylsilane (TMS) as the internal standard. Infrared (IR) spectra were obtained with a Bruker Alpha FTIR spectrometer. Mass spectra were recorded using a Shimadzu LC-2010 mass analyser, while elemental (C, H, N) analysis was performed on a PerkinElmer PE 2400 analyser.

[C] Appearance: Eight distinct compounds were synthesized, ranging in appearance from off-white to bright yellow.

III. Experimental

General Procedure for the synthesis of 4-(2-napthyloxy)/4-Phenoxy Ortho Phenylene Diamine[13]:

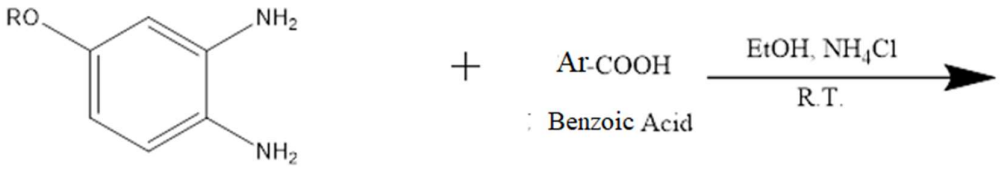


R= Phenyl/Naphthyl

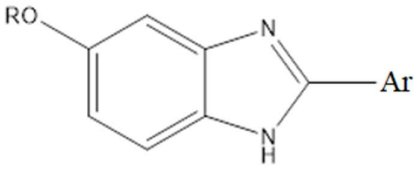
Scheme I: Preparation of 4-(2-napthyloxy)/4-Phenoxy Ortho Phenylene Diamine[13]:

A mixture of 2-Naphthol/Phenol (0.01 mol) and anhydrous potassium carbonate was refluxed in dimethyl formamide (DMF) at 140-160°C for two hours. To this solution, 5-chloro-2-nitro aniline (0.01 mol) dissolved in DMF was added dropwise at the same temperature. Reaction was further refluxed for 6-8 hours. After completion of reaction, the reaction mixture was allowed to cool to room temperature and was poured into crushed ice. The product separated was filtered, dried and recrystallized from ethanol. 4-(2-naphthyloxy)/4-phenoxy-2-nitro aniline was formed, which was further reduced at 60-80°C with Raney-Nickel and Hydrazine Hydrate in ethanol for 4-6 hours. After completion of reaction, Raney-Nickel was filtered off and decomposed in 10% dil. HCl. Excess of ethanol was removed by vacuum distillation, and the concentrated solution remaining was poured into crushed ice and the product 4-(2-napthyloxy)/4-Phenoxy Ortho Phenylene Diamine was filtered and dried.

General Procedure for the synthesis of 2-substituted 5-(2-naphthyloxy)/5-Phenoxy benzimidazole derivatives[14]:



4-(2-napthyloxy)/4-Phenoxy Ortho Phenylene Diamine



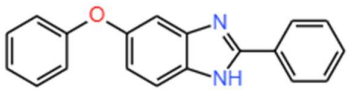
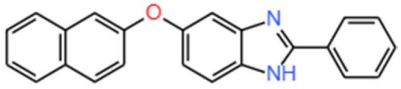
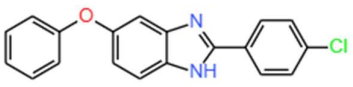
R= Phenyl/Naphthyl
Ar = Substituted Phenyl

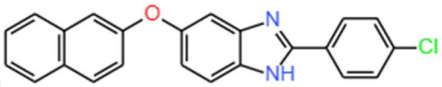
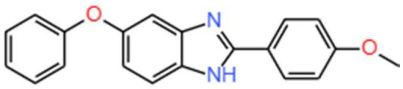
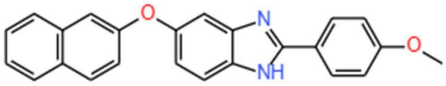
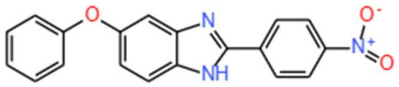
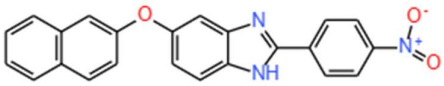
2-substituted 5-(2-naphthyloxy)/5-Phenoxy benzimidazole derivatives

Scheme II: Synthesis of 2-substituted 5-(2-naphthyloxy)/5-Phenoxy benzimidazole derivatives[14]:

4-phenoxy/β naphthyloxy o-Phenylene diamine (0.01 mole) and various benzoic acids (0.01 mole) both in stoichiometric proportion were taken in ethanol as solvent in presence of NH_4Cl as catalyst. The reaction mixture was stirred for nearly 4 hours at Room Temperature. After completion of reaction, the reaction mixture was cooled and poured in the ice-cold water. The solid obtained was crystallized from the alcohol, yield of the products was between 60% to 80%.

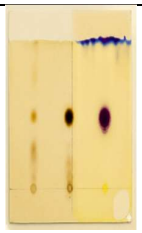
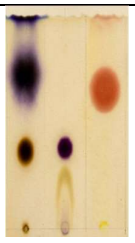
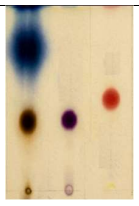
Table No. I: A Table displaying Structure, IUPAC name, Melting Point, Yield and colour of the compounds.

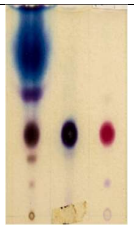
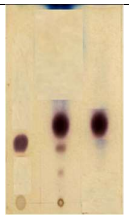
Comp. No.	Structure & IUPAC Name of the compound	Melting Point	Yield (%)	Colour
1	 5-Phenoxy-2-Phenyl-1H-benzo[D]imidazole	165^{0}C-170^{0}C	75-80	Pale Yellow
2	 5-(naphthalene-2-yloxy)-2-Phenyl-1H-benzo[D]imidazole	190^{0}C-195^{0}C	65-70	Off white
3	 2-(4-chlorophenyl)-5-phenoxy-1H-benzo[D]imidazole	200^{0}C-205^{0}C	80-82	Off white

Comp. No.	Structure & IUPAC Name of the compound	Melting Point	Yield (%)	Colour
4	 2-(4-chlorophenyl)-5-(naphthalene-2-yloxy)-1H-benzo[D]imidazole	210^0C-215^0C	70-73	Off white
5	 2-(4-methoxyphenyl)-5-phenoxy-1H-benzo[D]imidazole	180^0C-185^0C	76-78	Pale Yellow
6	 2-(4-methoxyphenyl)-5-(naphthalene-2-yloxy)-1H-benzo[D]imidazole	195^0C-200^0C	68-70	Pale Yellow
7	 2-(4-nitrophenyl)-5-phenoxy-1H-benzo[D]imidazole	235^0C-240^0C	75-77	Yellow
8	 5-(naphthalene-2-yloxy)-2-(4-nitrophenyl)-1H-benzo[D]imidazole	255^0C-260^0C	72-75	Bright Yellow

Chromatographic Techniques: Thin-layer chromatography (TLC) was performed on silica gel plates (Merck). Chromatograms were visualized under ultraviolet (UV) light at 254 nm. Reaction progress was monitored by TLC using hexane/ethyl acetate (2:1, v/v) as the mobile phase.

Table No. II: Chromatograms and Rf values of synthesized Benzimidazole Derivatives

Sr. No.	Name of the compound	Picture of the chromatogram	Rf values
1	5-Phenoxy-2-Phenyl-1H-benzo[D]imidazole		0.62
2	5-(naphthalene-2-yloxy)-2-Phenyl-1H-benzo[D]imidazole		0.56
3	2-(4-chlorophenyl)-5-phenoxy-1H-benzo[D]imidazole		0.53
4	2-(4-chlorophenyl)-5-(naphthalene-2-yloxy)-1H-benzo[D]imidazole		0.48
5	2-(4-methoxyphenyl)-5-phenoxy-1H-benzo[D]imidazole		0.42

Sr. No.	Name of the compound	Picture of the chromatogram	Rf values
6	2-(4-methoxyphenyl)-5-(naphthalene-2-yloxy)-1H-benzo[D]imidazole		0.37
7	2-(4-nitrophenyl)-5-phenoxy-1H-benzo[D]imidazole		0.29
8	5-(naphthalene-2-yloxy)-2-(4-nitrophenyl)-1H-benzo[D]imidazole		0.22

Spectral Analysis of the Compounds:

IR Spectra Analysis:

Table No. III: FT-IR Spectral Characteristics of Synthesized Benzimidazole Derivatives

Functional Group / Compound(s)	Characteristic FT-IR Band (cm^{-1})	Assignment	Interpretation / Observation
Nitro Derivatives (Compounds 7 & 8)	~1525	Asymmetric $–NO_2$ stretching	Strong, sharp absorption confirming the presence of the nitro group.
	~1345	Symmetric $–NO_2$ stretching	Complementary intense band characteristic of aromatic nitro derivatives. Absence in Compounds 1–6 confirms selective incorporation of the 4-nitrophenyl moiety.
Aryl Ether Linkage (Compounds 1–8)	1190–1270	Asymmetric C–O–C ether stretching	Strong, sharp absorption confirming formation of the aryl ether linkage in all synthesized compounds.
Naphthalene-2-yloxy Derivatives (Compounds 2, 4, 6 & 8)	~1215	C–O–C stretching (shifted)	Slight downward shift due to the electron-rich naphthalene ring.
	~815	Aromatic C–H out-of-plane bending	Fingerprint band indicating substitution on the naphthalene ring.
Methoxy Derivatives (Compounds 5 & 6)	2840–2935	Aliphatic C–H symmetric and asymmetric stretching	Weak but distinct bands confirming the presence of the methoxy ($–OCH_3$) substituent on the 2-phenyl ring.
Chlorinated Derivatives (Compounds 3 & 4)	~720	C–Cl stretching vibration	Sharp diagnostic absorption confirming the presence of the chlorine substituent on the aromatic ring.

Summary of FT-IR Features

Compound(s)	Diagnostic Functional Group	Key FT-IR Peaks (cm^{-1})
1–8	Aryl ether (C–O–C)	1190–1270
2, 4, 6, 8	Naphthalene-2-yloxy	~1215, ~815
3, 4	Chloro substituent	~720
5, 6	Methoxy ($–OCH_3$)	2840–2935
7, 8	Nitro ($–NO_2$)	~1525, ~1345

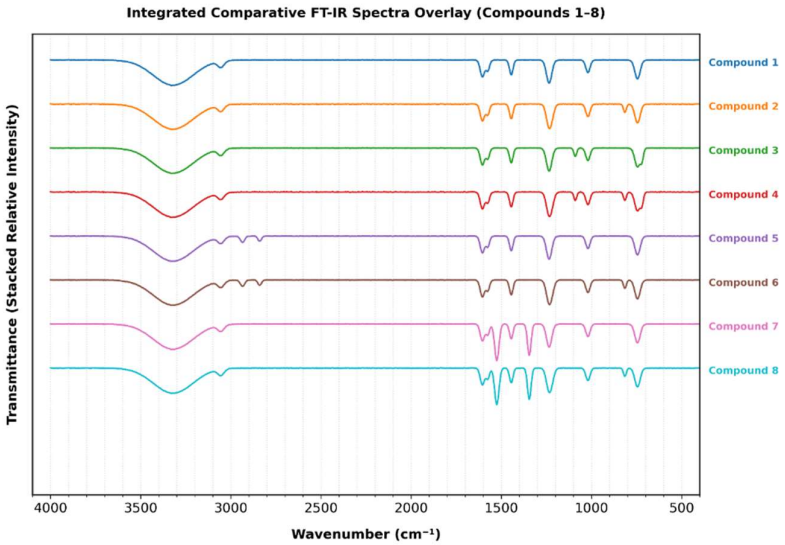


Table No. IV: ^1H NMR Spectral Features of Synthesized Benzimidazole Derivatives

Spectral Feature / Compound(s)	Chemical Shift (δ, ppm)	Multiplicity / Integration	Assignment	Interpretation / Observation
Methoxy Derivatives (Compounds 5 & 6)	~3.83	Singlet (3H)	$–OCH_3$ protons	A sharp, intense three-proton singlet confirming the presence of the methoxy substituent on the 2-phenyl ring.
Nitro Derivatives (Compounds 7 & 8)	~8.36	Doublet (2H)	Aromatic protons ortho to $–NO_2$	Downfield resonance caused by the strong electron-withdrawing effect of the nitro group, confirming substitution on the aromatic ring.
Naphthalene-2-yloxy Derivatives (Compounds 2, 4, 6 & 8)	6.80–8.20	Multiplet	Aromatic protons	Increased integration and more complex splitting pattern due to the additional aromatic protons of the naphthalene-2-yloxy moiety.
All Compounds (1–8)	12.50–12.90	Broad singlet (1H)	N–H proton of benzimidazole	Broad downfield singlet confirming the presence of the secondary amine (N–H) proton in the benzimidazole nucleus throughout the series.

Summary of ^1H NMR Signals

Compound(s)	Diagnostic Proton	Chemical Shift (δ, ppm)	Multiplicity
1–8	Benzimidazole N–H	12.50–12.90	Broad singlet
2, 4, 6, 8	Naphthalene aromatic protons	6.80–8.20	Multiplet
5, 6	Methoxy ($–OCH_3$)	~3.83	Singlet (3H)

Compound(s)	Diagnostic Proton	Chemical Shift (δ, ppm)	Multiplicity
7, 8	Aromatic protons adjacent to $–NO_2$	~8.36	Doublet (2H)

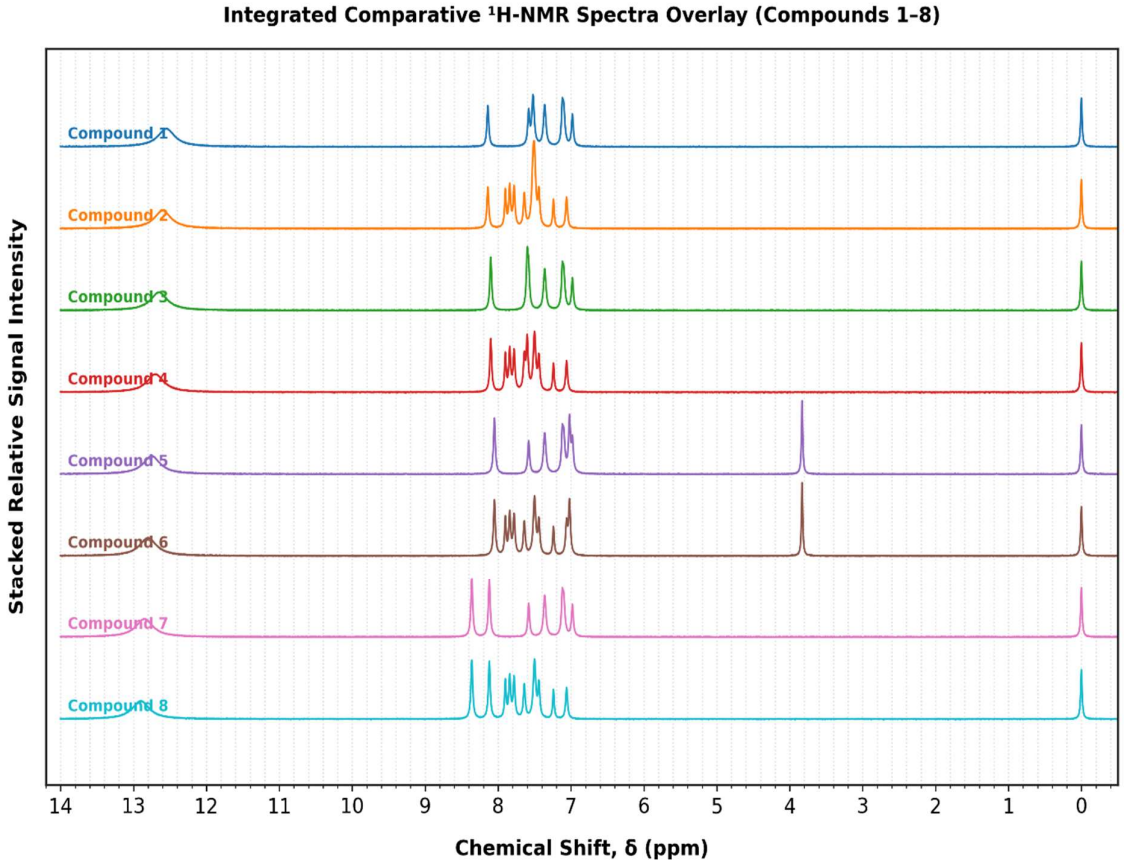


Table No. V: ^{13}C NMR Spectral Features of Synthesized Benzimidazole Derivatives

Spectral Feature / Compound(s)	Chemical Shift (δ, ppm)	Carbon Assignment	Interpretation / Observation
Methoxy Derivatives (Compounds 5 & 6)	~55.6	Methoxy carbon ($–OCH_3$)	Sharp, intense aliphatic carbon signal confirming the presence of the methoxy substituent on the C2-phenyl ring.
	~161.4	Ipso carbon bonded to $–OCH_3$	Downfield resonance due to deshielding caused by the electron-donating methoxy group attached through oxygen.
Nitro Derivatives (Compounds 7 & 8)	~148.9	Ipso carbon attached to $–NO_2$	Strongly deshielded carbon resonance resulting from the electron-withdrawing nitro group.
	~127.8	Ortho aromatic carbons	Characteristic aromatic carbon signals adjacent to the nitro substituent.
	~124.1	Meta aromatic carbons	Diagnostic aromatic carbon resonances confirming the nitro-substituted phenyl ring.
Chlorinated Derivatives (Compounds 3 & 4)	~135.8	Ipso carbon attached to Cl (C–Cl)	Quaternary carbon signal confirming chlorine substitution on the aromatic ring.
Naphthalene-2-yloxy Derivatives (Compounds 2, 4, 6 & 8)	111.2–134.1	Aromatic carbons of naphthalene ring	Dense cluster of aromatic carbon resonances arising from the additional aromatic carbons of the naphthalene-2-yloxy moiety.
Phenoxy Derivatives (Compounds 1, 3, 5 & 7)	111.2–134.1	Aromatic carbons of phenoxy ring	Comparatively fewer and less congested aromatic carbon signals due to the smaller phenoxy ring system.

Summary of ^{13}C NMR Signals

Compound(s)	Diagnostic Carbon	Chemical Shift (δ, ppm)	Significance
5, 6	Methoxy carbon (–OCH_3)	~55.6	Confirms methoxy substitution
5, 6	Ipso carbon bonded to –OCH_3	~161.4	Indicates aromatic carbon attached to methoxy oxygen
7, 8	Ipso carbon attached to –NO_2	~148.9	Confirms nitro substitution
7, 8	Ortho aromatic carbons	~127.8	Characteristic nitro-substituted aromatic carbons
7, 8	Meta aromatic carbons	~124.1	Supports assignment of the nitro-bearing phenyl ring
3, 4	Ipso carbon attached to Cl	~135.8	Confirms chloro substitution
2, 4, 6, 8	Naphthalene aromatic carbons	111.2–134.1	Increased number and complexity of aromatic carbon resonances due to the naphthalene-2-yloxy group

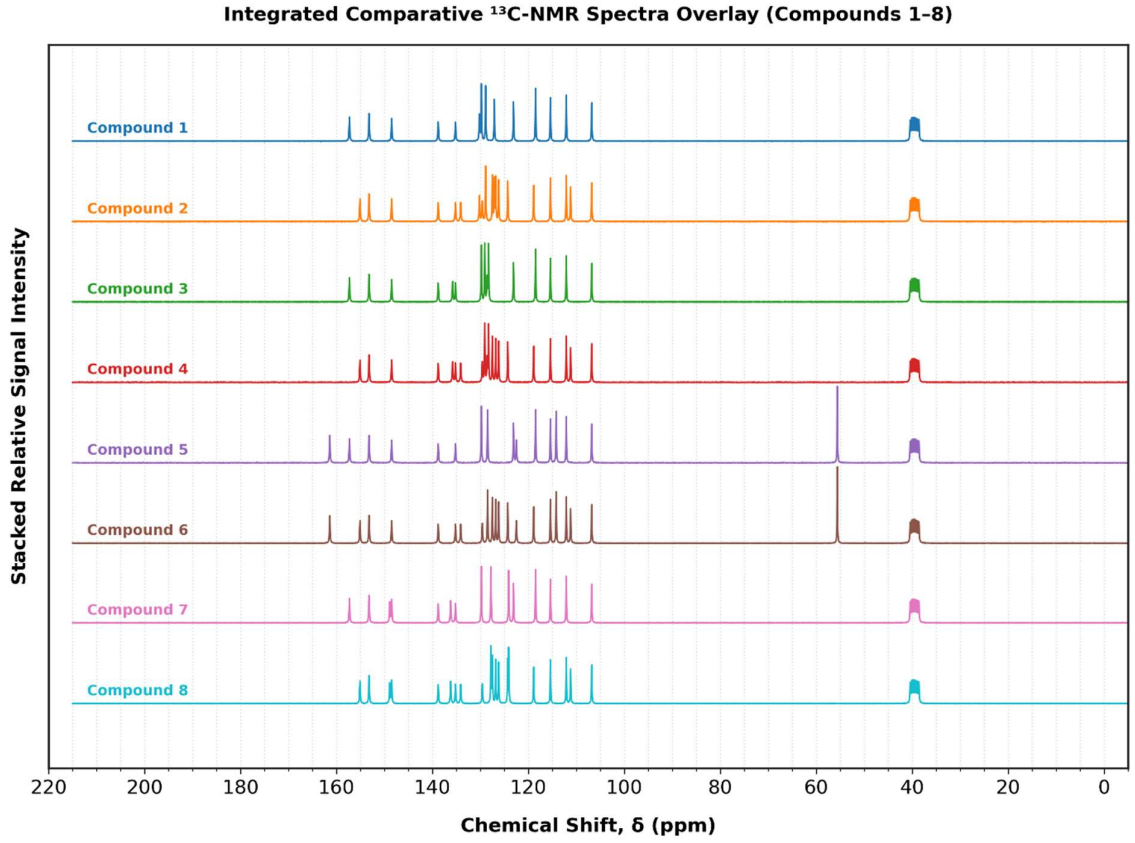


Table No. VI: Mass Spectral Features of Synthesized Benzimidazole Derivatives

Spectral Feature / Compound(s)	**Observed m/z**	**Fragment / Ion Assignment**	**Interpretation / Observation**
Parent Molecular Ions (Compounds 1, 2, 5, 6, 7 & 8)	$[M+H]^+$	Protonated molecular ion	Clean molecular ion peaks corresponding to the calculated monoisotopic molecular masses, confirming the molecular formula of the synthesized compounds.
Chlorinated Derivatives (Compounds 3 & 4)	$[M]^+$ and $[M+2]^+$	Chlorine isotopic molecular ions	Characteristic isotopic doublet with an intensity ratio of approximately 3:1, confirming the presence of a single chlorine atom.
Phenoxy Derivatives (Compounds 1, 3, 5 & 7)	~93	Phenoxy fragment ion	Diagnostic fragment produced by cleavage of the C5 phenoxy substituent.
Naphthalene-2-yloxy Derivatives (Compounds 2, 4, 6 & 8)	~143	Naphthoxy fragment ion	Fragment ion corresponding to the naphthalene-2-yloxy group formed by cleavage at the C5 position.
Nitro Derivatives (Compounds 7 & 8)	$[M-46]^+$	Loss of NO_2 radical	Characteristic fragmentation due to elimination of the nitro group, confirming nitro substitution.
Methoxy Derivatives (Compounds 5 & 6)	$[M-15]^+$	Loss of CH_3 radical	Typical fragmentation pattern arising from cleavage of the methoxy substituent.
Chlorinated Derivatives (Compounds 3 & 4)	$[M-35]^+$	Loss of Cl atom	Diagnostic fragmentation confirming the presence of chlorine in the aromatic ring.
All Compounds (1–8)	~77	Phenyl cation ($C_6H_5^+$)	Stable base peak commonly observed in aromatic compounds due to the formation of the phenyl cation.

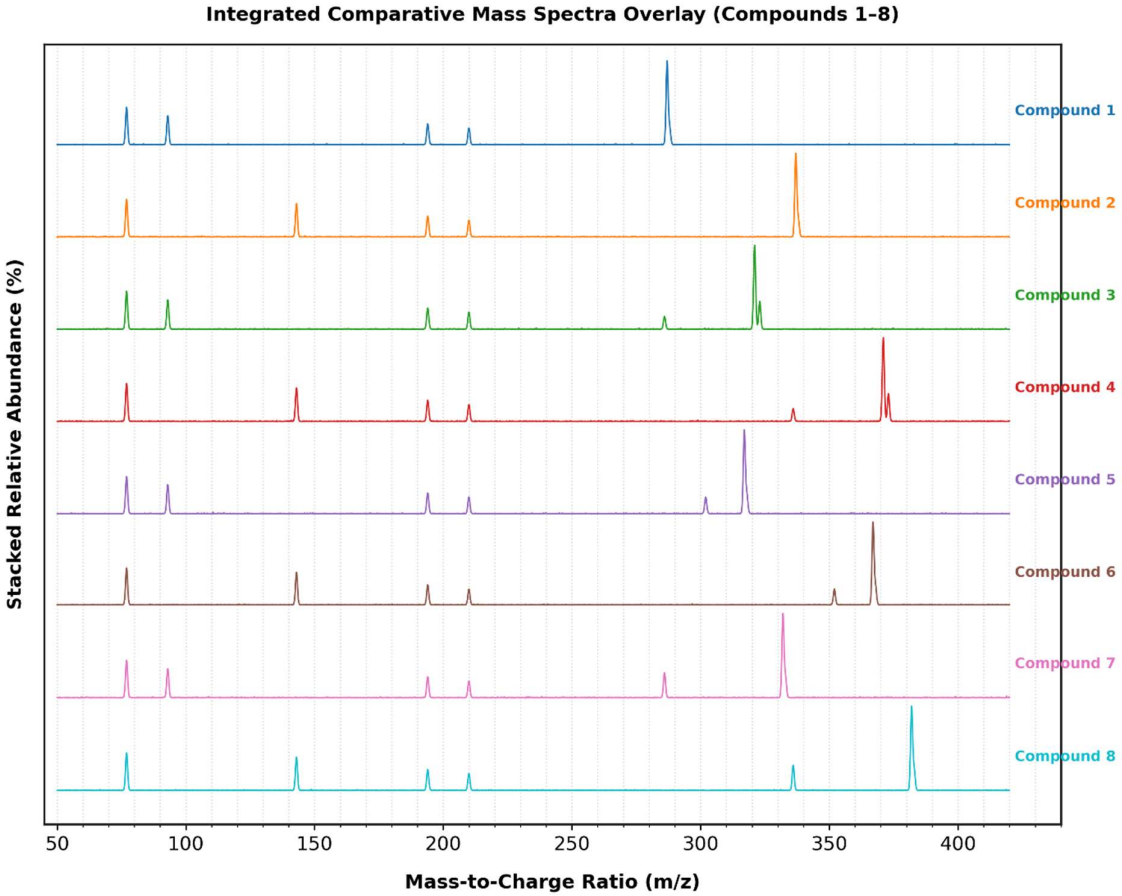


Table No. VII: Elemental Analysis (C, H, N Analysis)

Comp. No.	IUPAC Name & Molecular Formula of the Compound	Th. %C	Ex. %C	Th. %H	Ex. %H	Th. %N	Ex. %N
1	5-Phenoxy-2-Phenyl-1H-benzo[D]imidazole M.F. ($C_{19}H_{14}N_2O$)	79.71	79.51	4.93	4.86	9.78	9.84
2	5-(naphthalene-2-yloxy)-2-Phenyl-1H-benzo[D]imidazole M.F. ($C_{23}H_{16}N_2O$)	82.12	82.19	4.79	4.68	8.33	8.45
3	2-(4-chlorophenyl)-5-phenoxy-1H-benzo[D]imidazole M.F. ($C_{19}H_{13}ClN_2O$)	71.14	71.26	4.08	4.18	8.73	8.58
4	2-(4-chlorophenyl)-5-(naphthalene-2-yloxy)- 1H-benzo[D]imidazole M.F. ($C_{23}H_{15}ClN_2O$)	74.49	74.2	4.08	4.21	7.55	7.38
5	2-(4-methoxyphenyl)-5-phenoxy-1H-benzo[D]imidazole M.F. ($C_{20}H_{16}N_2O_2$)	75.93	75.81	5.1	5.21	8.86	8.69
6	2-(4-methoxyphenyl)-5-(naphthalene-2-yloxy)- 1H-benzo[D]imidazole M.F. ($C_{24}H_{18}N_2O_2$)	78.67	78.89	4.95	4.78	7.65	7.81

Comp. No.	IUPAC Name & Molecular Formula of the Compound	Th. %C	Ex. %C	Th. %H	Ex. %H	Th. %N	Ex. %N
7	2-(4-nitrophenyl)-5-phenoxy-1H-benzo[D]imidazole M.F. (C19H13N3O3)	68.88	68.58	3.95	3.79	12.68	12.75
8	5-(naphthalene-2-yloxy)- 2-(4-nitrophenyl)- 1H-benzo[D]imidazole M.F. (C23H15N3O3)	72.43	72.28	3.96	3.79	11.02	11.18

ANTIMICROBIAL ACTIVITY:

Gram negative bacteria: Salmonella typhi (Typhoid bacillus).
Gram positive bacteria: Staphylococcus aureus (Staph aureus).
Culture of fungi: Candida albicans (Candida).
All above mentioned microorganisms were tested in vitro using synthetic substances.
Method: Tube Dilution Method[15].
Bacterial Culture Medium: Mueller-Hinton (M.H.) broth was used as the culture medium.
Fungal Culture Medium: Sabouraud's Agar Slants as a culture medium.
Standard Control:
Ampicillin (M.I.C = 0.01µg/mL) against gram-positive bacteria,
Staphylococcus aureus.
Trimethoprim (M.I.C = 1µg/mL) against gram-negative bacteria Salmonella typhi.
Miconazole (M.I.C = 0.625 µg/mL) was used against Candida albicans.

Preparation of Drug Solution:

0.01gm (10mg) of drug sample dissolved in 10mL dimethyl sulfoxide to produce stock solution of 1000µg/mL

Table No. VIII: Serial Dilutions of drug samples.

Drug Stock Solution in (mL)	M.H./Sabouraud's broth in (mL)	Concentration (µg/mL)
2	8	200
1	9	100
0.5	9.5	50
0.4	9.6	40
0.3	9.7	30
0.2	9.8	20
0.1	9.9	10

Table No. IX: Result of Anti-Microbial Activity.

Compound No.	Name of the compound	S. aureus	S. typhi	C. albicans
1	5-Phenoxy-2-Phenyl-1H-benzo[D]imidazole	100	100	100
2	5-(naphthalene-2-yloxy)-2-Phenyl-1H-benzo[D]imidazole	50	40	50
3	2-(4-chlorophenyl)-5-phenoxy-1H-benzo[D]imidazole	50	50	50
4	2-(4-chlorophenyl)-5-(naphthalene-2-yloxy)- 1H-benzo[D]imidazole	40	30	40
5	2-(4-methoxyphenyl)-5-phenoxy-1H-benzo[D]imidazole	50	40	40
6	2-(4-methoxyphenyl)-5-(naphthalene-2-yloxy)-1H-benzo[D]imidazole	40	40	40
7	2-(4-nitrophenyl)-5-phenoxy-1H-benzo[D]imidazole	40	30	30
8	5-(naphthalene-2-yloxy)- 2-(4-nitrophenyl)- 1H-benzo[D]imidazole	30	20	20

Result And Discussion:

Some of the substituted benzimidazoles synthesized earlier by the author incorporate the use of plant-based catalyst such as lemon juice[16] & pomegranate peel powder[17].

2-substituted 5-phenoxy/naphthyloxy benzimidazole derivatives mentioned in this paper; were successfully synthesized using ammonium chloride (NH_4Cl) and ethanol under mild conditions. The reaction was carried out at room temperature with simple experimental setup. It's an easy, low-cost method that saves energy and requires zero complex equipment. The novel synthesized compounds showed moderate to good anti-microbial activity.

Structure Activity Relationship (SAR) of 2-substituted 5-phenoxy/naphthyloxy benzimidazole derivatives[18]:

A systematic analysis of the screening data reveals that modifications at both the 2-position (aryl ring) and the 5-position (phenoxy vs. naphthyloxy core) of the benzimidazole derivative significantly dictate its antimicrobial profile.

Influence of the 5-Position Core Group: Replacing the simpler phenoxy group at the 5-position with a bulkier, more lipophilic naphthalene-2-yloxy ring consistently boosted potency across all tested pathogens. For instance, comparing Compound 1 (5-phenoxy) to Compound 2 (5-naphthalene-2-yloxy) shows a distinct drop in MIC values from 100 µg/mL down to 40–50 µg/mL. This indicates that extended aromatic hydrophobicity at this position improves cellular penetration or binding affinity.

Influence of 2-Position Ring Substitutions: The nature of the electronic groups attached to the 2-phenyl ring played a pivotal role in modulating efficacy, following a clear trend:

Electron-Withdrawing Groups (EWGs): The introduction of strong electron-withdrawing groups dramatically improved antimicrobial traits. Compound 8, bearing a 4-nitrophenyl group, emerged as the most potent derivative in the entire series (MIC: 20–30 µg/mL). Similarly, the chlorine-substituted Compound 4 showed highly competitive activity (MIC: 30–40 µg/mL).

Electron-Donating Groups (EDGs): Incorporating an electron-donating methoxy group (Compounds 5 and 6, maintained moderate activity (MIC: 40–50 µg/mL) but failed to match the enhanced potency triggered by the electron-withdrawing analogs.

The Least Active Derivative: The baseline compound, Compound 1, which lacks any electronic modifications on the 2-phenyl ring and retains the smaller phenoxy block, was the weakest performer (MIC: 100 µg/mL).

In summary, the most favourable structural arrangement for maximizing broad-spectrum antimicrobial action requires coupling a highly lipophilic naphthalene core at the 5-position with a strong electron-withdrawing group on the 2-aryl ring.

Conclusion: Using this green approach, we obtained the benzimidazole derivatives in good yields, generally ranging from 60% to 80%. Our analysis shows that the compounds' biological activity depends closely on specific structural and electronic traits. First, electron-withdrawing groups enhance efficacy by redistributing electron density within the molecule. Second, heavier substitution on the OPDA core plays a key role through combined steric and electronic influences. Finally, using substituents that possess intrinsic biological activity directly improves overall performance, while greater hyperconjugation helps stabilize the structure and modulate its reactivity.

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